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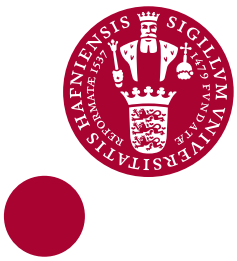

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Measles, mumps, and rubella vs diphtheria-tetanus-acellular-pertussis-inactivated-polio-*Haemophilus-influenzae*-type-b as the most recent vaccine and risk of early "childhood asthma"

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Key words: Asthma; Immunity, Heterologous; Immunization; Measles-Mumps-Rubella Vaccine; Non-specific effects of vaccines; Infant, Asthma; Vaccine-sequence; Trained innate immunity

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Abstract

Background and objective: Live vaccines may have beneficial non-specific effects. We tested whether the live measles, mumps and rubella (MMR) vaccine compared with the non-live diphtheria-tetanus-acellular-pertussis-inactivated-polio-*Haemophilus-influenzae*-type-b (DTaP-IPV-Hib) vaccine as the most recent vaccine was associated with less childhood asthma and fewer acute hospital contacts for childhood asthma among boys and girls.

Methods: This study is a nationwide register-based cohort study of 338 761 Danish children born 1999-2006. We compared 1) the incidence of first-registered childhood asthma based on hospital contacts and drug prescriptions and 2) the incidence of severe asthma defined as acute hospital contacts for childhood asthma between 15 and 48 month among children who latest had received 3 doses of DTaP-IPV-Hib and then MMR with children who latest had received 3 doses of DTaP-IPV-Hib.

Results: For boys, following the recommended vaccine schedule of MMR after DTaP-IPV-Hib3 compared with DTaP-IPV-Hib3 as the latest vaccine, MMR was associated with 8.0 (95% confidence interval 3.9-12.2) fewer childhood asthma cases per 1,000 boys, corresponding to 10% (5-15%) reduction in the cumulative incidence of childhood asthma. MMR, when given last, was also associated with 16.3 (12.7-19.9) fewer acute hospital admissions for childhood asthma per 1,000 boys, corresponding to a 27% (22-31%) reduction in the cumulative incidence. No associations were seen for girls.

Conclusion: MMR may have a protective effect against childhood asthma for boys. This calls for an understand of whether non-specific effects of vaccines can be used to optimise our vaccine programmes.

Key Messages

- The live measles, mumps and rubella (MMR) vaccine as the most recently received vaccine may reduce childhood asthma.
- In a Danish population of children aged 15-48 months, the measles, mumps and rubella vaccine compared with the non-live diphtheria-tetanus-acellular-pertussis-inactivated-polio-haemophilus-influenzae-type-b vaccine (DTaP-IPV-Hib) as the most recent vaccine was associated with less childhood asthma and less severe asthma for boys.
- Timely MMR after DTaP-IPV-Hib may protect one in 124 (95% CI 82 to 260) boys in the age between 15-48 months from childhood asthma.
- This potential calls for a better understanding of non-specific effects of vaccines.

Introduction

Vaccines may have beneficial non-specific effects (NSEs).(1-4) Live vaccines affect the innate immune system beneficially leading to increased response to unrelated pathogens(2) and are associated with lower morbidity and mortality from non-targeted diseases. (1,3-7) Studies suggest that live vaccines induce a T-helper 1 cell dominant shift reducing atopic diseases.(4,8,9) In contrast, non-live vaccines can induce tolerance of the innate immune system leading to decreased responses to unrelated pathogens(2) and have been associated with higher morbidity and mortality from non-targeted diseases.(1,3-7) The non-specific effects of live vaccines are most pronounced as long as a given vaccine is the most recent vaccine and may vary by sex.(4,8,9)

Studies of the live measles, mumps, and rubella (MMR) vaccine and childhood asthma have reported preventive effects(10-13), detrimental effects(14) or no effect(15-19). However, vaccination sequence was not assessed in any of the studies (10-19) and sex-differential effects was only assessed in one study(11).

The main objective of this study was to test the hypothesis that the live MMR vaccine *as the most recent vaccine* compared with the non-live diphtheria-tetanus-acellular pertussis-polio-*Haemophilus Influenzae* type b (DTaP-IPV-Hib) vaccine is associated with a lower incidence of childhood asthma defined by hospital contacts and drug prescriptions in Danish children aged 15 to 48 months (hypothesis 1). Our secondary objective was to test whether MMR was

associated with a lower incidence of *severe* childhood asthma defined by acute hospital contacts (hypothesis 2). We examined whether associations differed by sex.

Method

This study is a register-based cohort study of Danish children followed from the age of 15 months until the age of 48 months for the risk of childhood asthma according to whether their last vaccine received was DTaP-IPV-Hib. Linkage across Danish nation-wide registers is possible using Danish personal identification numbers assigned to all new-borns. We used information from The Danish Civil Registration System, the Danish National Health Service Register, the Danish National Patient Register, the Danish National Prescription Register, the Danish Medical Birth Register, and information from Statistics Denmark (Supplementary information 1).

Study base and vaccinations

To reduce interference from other vaccines than MMR and DTaP-IPV-Hib, the study base was children born in Denmark from 1 July 1999 until and including 30 September 2006 and followed from 15 months of age until 48 months of age (Supplementary figure 1). For this study base, the Danish childhood vaccination programme until 48 months of age was three doses of the non-live DTaP-IPV-Hib at 3, 5, and 12 months of age and the first dose of the live MMR at 15 months of age.

In Denmark, vaccines are administered free-of-charge by the general practitioners. For the purpose of reimbursement, information about vaccine type, dose, and week of vaccination is collected in the Danish National Health Service Register.(20)

Childhood asthma

Asthma in young children may be differentiated by multiple phenotypes(21) and multiple ways of phenotyping.(22) Asthma, asthmatic bronchitis and infection induced wheezing in young children are difficult to separate using register data, hence we used the term "childhood asthma" to cover the aforementioned diseases.

Childhood asthma was defined by information from two sources: 1) the Danish National Patient Register(23) holds information on hospital contacts coded with the 10th version of the international classification of diseases (ICD-10); 2) The Danish National Prescription Register(24) holds information about all redeemed prescriptions in Danish pharmacies.

The main outcome (hypothesis 1) was the incidence of first-registered childhood asthma between 15 to 48 months of age defined as the first registration of a hospital contacts (outpatients, inpatients, and emergency room) according to ICD-10 codes J45 (*Asthma*) and J46 (*Status asthmaticus*) or the first prescription of inhaled glucocorticoids (R03BA) or montelukast (R03DC03) (at least 2 prescriptions of either glucocorticoids or montelukast within 12 months). Our second outcome (hypothesis 2) was severe childhood asthma between 15 to 48 months of age defined as the incidence of all acute hospital contacts (inpatients and emergency room

visits) with ICD-10 codes J45 or J46. Allowing for recurrent events, adjacent acute hospital contact periods within 5 days of last hospital discharge counted as one acute hospital contact.

Inclusion and exclusion criteria

To ensure that the study population consisted of children, who followed the vaccination schedule before the baseline of our study, only children who had received the first two doses of DTaP-IPV-Hib before the age of 11 months were included. For hypothesis 1, we excluded children who had been registered with childhood asthma before 15 months of age, while this restriction did not apply for hypothesis 2, since it focused on repeated events (Figure 1 and Supplementary figure 2).

Sequence cohorts

A proportion of Danish children deviate from the recommended schedule of the childhood vaccination programme. This variation allows us to investigate the robustness of the analyses in three partly overlapping vaccine sequence cohorts (Figure 1); *recommended sequence* (DTaP-IPV-Hib1-3-then-MMR vs DTaP-IPV-Hib1-3 only), *early MMR sequence* (DTaP-IPV-Hib1-2-then-MMR vs DTaP-IPV-Hib1-2 only) and *interrupted sequence* (DTaP-IPV-Hib1-2-then-MMR vs DTaP-IPV-Hib1-2-then-MMR-then-DTaP-IPV-Hib3).

Follow-up

For hypothesis 1, all children entered the study at the first Sunday after they turned 15 months of age or when their vaccination sequence qualified them for one of the sequence cohorts described above, whichever occurred last. All children left the study: a) at the date of a registered childhood asthma event, b) at 48 months of age, c) when receiving more than one vaccine in one day or receiving unrelated vaccines, or d) 12 months before emigrating or dying, to allow two prescriptions to be registered within a year, whichever occurred first. For hypothesis 2, the same entry and exit criteria applied, except that children registered with an acute hospital contact for childhood asthma left the study for 5 days and re-entered the study to make sure that we did not count one episode several times.

Statistical methods

We suspected that hospital admissions due to infectious diseases could both affect vaccination status(25,26) and later childhood asthma(27,28); furthermore hospital admissions due to infectious diseases have been shown to be reduced by prior MMR vaccination(4,29) (illustrated in Supplementary figure 3). This is known as time-varying confounding. We attempted to control for this potential issue using weights, which we updated each week based on 22 covariates (Supplementary information 1 and 2). Such an approach is well-established and aims at creating comparable comparison groups at any given time during follow up.(30,31) We have added a technical description in Supplementary information 2.

We calculated the crude and weighted cumulative incidence rates and reported the cumulative incidence rate reduction per 1,000 children for each group at 48 months of age ($wIRreduction_{48}$) and cumulative incidence rate ratios at 48 months of age. Standard errors were calculated using robust estimators and confidence intervals were estimated with 2.5% and 97.5% quantiles using 100,000 simulations. The analyses assumed independent observations. A spline function of the crude and weighted cumulative incidence rates were plotted for each analysis. We investigated whether the $wIRreduction_{48}$ were different for girls and boys. Additionally, to compare with hazards ratios often reported in the medical literature, we used a weighted Cox proportional hazards model to estimate hazard ratios. The weighted Cox proportional hazards model had age as the underlying time scale and was stratified by week (Sunday to Saturday) of birth thereby adjusting for the effect of age and calendar time. We tested the assumption of proportional hazards using Schoenfeld residuals.

Sensitivity analysis

Since infections may affect childhood asthma(27,28) and MMR has been associated with fewer infections in the same cohort(4), we conducted a sensitivity analysis excluding hospital admissions with childhood asthma co-occurring with hospital admissions for an infectious disease, to ensure we did not partly reproduce earlier results.

If childhood asthma was registered using two prescriptions within one year, we used the first date of two prescriptions. Thus, the registered childhood asthma date was conditioned on a

110 future prescription, which could cause a collider bias introducing a non-causal association
111 between MMR vaccination and the first prescription for childhood asthma. We conducted a
112 sensitivity analysis using the second date of prescriptions.

113 Furthermore, we conducted a sensitivity analysis of the effect of DTaP-IPV-Hib 3 vs DTaP-IPV-
114 Hib 2 from 12 to 15 months of age under the hypothesis that the incidence of new-onset
115 childhood asthma and severe asthma would not differ. If DTaP-IPV-Hib 3 is associated with a
116 reduced incidence of asthma compared with DTaP-IPV-Hib 2 in spite of adjustment for
117 potential confounding, this would suggest that we have been unable to fully control for
118 confounding i.e. that the most healthy children receive the next vaccine (residual confounding
119 of a "healthy vaccinee effect" -bias)Data was analysed using Stata 14.0 and R 3.3.1 with version
120 1.0-11 for the ipw package. Register based studies do require ethical approval by the Danish
121 Central Scientific Ethics Committee.

122 Results

123 From the study base of 467,919 children, 338,761 children were eligible for studying hypothesis
124 1 (Figure 1) and 364,270 children were eligible for hypothesis 2 (Supplementary figure 2). The
125 recommended sequence included the majority of risk time with 773,054 person years of follow
126 up (pyrs), the early MMR sequence had 50,918 pyrs, and the interrupted sequence had 36,788
127 pyrs.

Most shifts in vaccination sequence cohorts happened between 15-20 months of age (Supplementary figure 4 and 5). Childhood asthma peaked at 8 months of age, and boys have a higher incidence than girls (Supplementary figure 6). Among the recommended sequence for hypothesis 1, 18 776 children were registered with childhood asthma during follow-up (of which; 25% based on hospital contacts, 74% based on glucocorticoids, and 1% based on montelukast).

Covariates were approximately similarly distributed between vaccination sequence groups at 16 months of age (Supplementary table 1). However, children who had received only DTaP-IPV-Hib 1 + 2 at 16 months of age tended to have a skewed distribution compared with the remaining vaccination sequence groups especially regarding single parenthood, family income, maternal education, other children in the household, mother smoking during pregnancy, and previous infectious diseases and prescribed antibiotics.

For hypothesis 1, MMR compared with DTaP-IPV-Hib as most recent vaccine was associated with a weighted cumulative incidence reduction of childhood asthma per 1,000 children at 48 months of age ($wIRreduction_{48}$) of 4.5 (95% confidence interval (CI) 1.7 to 7.2), 3.8 (95% CI -3.3 to 10.8), and 22.9 (95% CI 3.1 to 42.7) for *the recommended, early, and interrupted sequence respectively* (Table 1). The incidence diverged mostly in the first part of follow-up (Figure 2). The incidence difference tended to be larger among boys than girls (Table 2).

For hypothesis 2, MMR compared with DTaP-IPV-Hib as the last received vaccine was associated with a wIRreduction$_{48}$ of 8.2 (95% CI 6.0 to 10.5), 13.4 (95% CI 7.3 to 19.4), and 1.7 (95% CI -11.8 to 15.2) for the rate of acute hospital contacts for childhood asthma in the *recommended, early and interrupted sequence* (Table 3 and figure 3). Again, the association was strongest among boys compared with girls in the recommended sequence (Table 4).

When analysing the hypotheses using hazard ratios, the assumption of proportional hazards was not met for hypothesis 1 (Supplementary table 2) but was more stable for hypothesis 2 (Supplementary table 3).

Excluding concurrent hospital contacts for infectious diseases and using the date of the second prescription provided similar estimates (Supplementary tables 4, 5 and 6).

The weighted cumulative incidence difference from 12 to 15 months of age per 1,000 children for DTaP-IPV-Hib 3 compared with DTaP-IPV-Hib 2 for the hypothesis 1 and 2 outcomes were respectively 2.7 (95% CI 1.6 to 3.8) and 0.6 (95% CI -0.1 to 1.3). The association tended to be stronger among boys than girls (Supplementary tables 7 and 8).

Discussion

Among boys but not girls, MMR vaccination compared with DTaP-IPV-Hib as the last received vaccine across cohorts was associated with a lower incidence of childhood asthma and fewer acute hospital contacts for childhood asthma.

Strengths and weaknesses

This was a large nationwide study and we applied state of the art statistical methods, the weighted approach, to handle potential time-varying confounding.(32) The weights were not extreme so no single individual affected the results disproportionally (Supplementary figure 7). The 95% confidence interval for the incidence rate difference was calculated assuming independent observations, which is a limitation as children have contributed risk time to both vaccination groups.

By ensuring that children had followed the vaccination programme (received DTaP-IPV-Hib 1 and 2 before 11 months of age) we increased homogeneity of the study population(33) and by including many potential confounders, we may to some extent have controlled for unmeasured confounding though it cannot be ruled out. Potential time-varying confounding due to children' s health status was modelled by previous chronic diseases as well as hospital admissions and antibiotic use for infectious diseases. The comparison between DTaP-IPV-Hib 3 and DTaP-IPV-Hib 2 for the hypothesis 1 and to some degree hypotheses 2 suggests that there may be confounding not fully adjusted for (residual confounding of a "*healthy vaccinee effect*" -bias). However, in the *interrupted sequence* cohort, children who received the next vaccine (DTaP-IPV-Hib 3 after MMR) had a higher risk for childhood asthma compared with those who had only received MMR, which indicates that a "*healthy vaccinee effect*" -bias does not fully explain our results Receiving the MMR vaccine as the last vaccine was associated with approximately similar cumulative incidence rates across sequences, while DTaP-IPV-Hib in

contrast was associated with greater cumulative incidence rates. As this pattern was independent of which sequence children followed, it suggests that both vaccines affect the risk of childhood asthma respectively beneficially and detrimentally.

MMR vaccination coverage in Denmark may be underreported,(34) which would increase proportionally with time if MMR vaccinated children stay categorised as DTaP-IPV-Hib 3 vaccinated thus biasing the estimate towards null over time – a pattern we also observed. The inclusion criteria DTaP-IPV-Hib 1 and 2 before 11 months of age decreased the misclassification of the reference groups in the *recommended sequence* and *early MMR sequence.* Unsystematic underreporting would also cause conservative estimates. Simultaneous administration of vaccines was outside the scope of our analysis.

Neither of our sensitivity analyses indicated that we should have reached other conclusions. Further analyses indicated that it was the first prescription of childhood asthma prescription rather than the criteria of two prescriptions within one year that captured the effect of MMR on childhood asthma (analysis not shown).

Studies on MMR and childhood asthma

No randomised trial has studied the effect of MMR on the risk of childhood asthma; nine diverse observational studies on the effect of MMR or measles vaccines on childhood asthma show conflicting results (Supplementary table 9). (10-19) The nine studies vary from large prospective cohort studies to small cross-sectional studies and represent children from 11

203 countries (two sets of studies partly overlap in study populations[(16,17) and (18,19)] and one
204 study partly overlap with the study population of our study(11)). The studies were further
205 heterogenic with regards to outcome definition, age group and sequence of vaccines.
206 Specifically, our study indicated that the effect of vaccine status on the incidence of childhood
207 asthma decreased with age, making comparisons for unlike age groups problematic. Our study
208 is the first study to strictly investigate the effect of having MMR as the most recent vaccine on
209 the risk of childhood asthma. Not differentiating the vaccine sequence mixes effects of multiple
210 vaccine combinations,(35) a problem, which was highlighted in a recent WHO review of non-
211 specific effects of vaccines(3) and also supported by this study. Furthermore, applying the
212 inclusion criteria where all children had received the first two doses of DTaP-IPV-Hib before 11
213 months of age increased the exchangeability of the comparison groups in our study compared
214 with the previous studies. Despite differences in design, the study overlapping with the study
215 population of our study found similar effects of MMR on the use of glucocorticoids and for
216 hospital admissions due to asthma.(11) However, they did not find similar sex differential
217 effects for hospital admissions due to asthma, which may have been masked by the effects of
218 other vaccines.

219 **Biological mechanisms**

220 Successful immunisation by live vaccines, like natural infections, has been shown to shift from a
221 predominant and often hyper reactive T-helper 2 cell to being T-helper 1 cell predominant that

allows an accelerated clearance of infections,(1) and thus a potentially reduced risk of childhood asthma.

MMR compared with DTaP-IPV-Hib as the most recent vaccine has been associated with fewer admissions for infectious diseases.(4) Since persistent respiratory infections may destroy epithelial cells of the respiratory tract making children with childhood asthma more prone to severe episodes(36) and as respiratory infections can function as irritants exaggerating wheeze attacks(9), then a reduction in infectious diseases could lead to a lower risk of childhood asthma.

Recent cutting edge immunological research show that live vaccines can train the innate immune system for swifter clearance of non-related pathogens possible through epigenetic reprogramming.(2) In accordance with our results indicating that males benefited more from the MMR vaccine, a new immunological study of Gambian children showed that measles vaccine was associated with enhanced proinflammatory innate responses for males but not for females possibly by modifying signaling via Toll-like receptor 4 (TLR4).(37) The duration of trained immunity is yet unknown, but according to our data the absolute risk difference was proportionally largest the first 10-15 months after vaccination and waned off (Figures 2 and 3).

Conclusion

Our study indicated that boys experience less childhood asthma and fewer acute hospital contacts for childhood asthma when the live MMR vaccine compared with the non-live DTaP-

IPV-Hib vaccine was the most recent vaccine. Data did not convincingly suggest an effect for girls. For now, these results are only indications, thus we hope other research groups will test our findings that MMR compared with DTaP-IPV-Hib as most recent vaccine reduces the risk of childhood asthma among boys and investigate why girls may not experience the same benefit. If supported, the question of whether a beneficial effect of MMR would persist or be countered by a subsequent non-live vaccine should be addressed.

If our estimates are correct then for 1,000 boys following the recommended vaccine schedule and receiving MMR timely after DTaP-IPV-Hib, MMR prevents 8.0 (95% CI 3.9 to 12.2) childhood asthma cases between 15 months and 48 months. Thus, one childhood asthma case is prevented for each 124 (95% CI 82 to 260) MMR vaccinations administrated. Though most childhood asthma cases occurred before 15 months of age in this study, potential immune modulation via MMR or other approaches for preventing childhood asthma calls for a better understanding of non-specific effects of vaccines.(38)

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